ORGANIC LETTERS

2010
Vol. 12, No. 22
5322−5325

Coupling the Petasis Condensation to an Iron(III) Chloride-Promoted Cascade Provides a Short Synthesis of Relenza Congeners

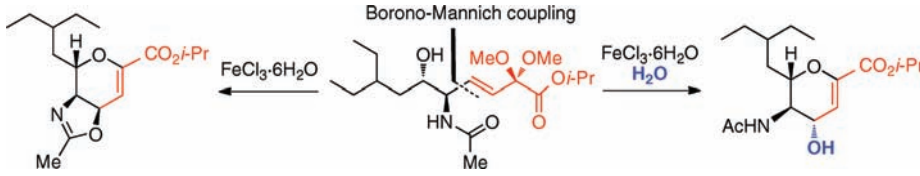
Jean-François Soulé,[†] Aurélie Mathieu,[†] Stéphanie Norsikian,*[,†] and Jean-Marie Beau*[,†,‡]

Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, F-91198 Gif-sur-Yvette, France, and Université Paris-Sud, Institut de Chimie Moléculaire et des Matériaux, F-91405 Orsay, France

jean-marie.beau@u-psud.fr; stephanie.norsikian@icsn.cnrs-gif.fr

Received September 27, 2010

ABSTRACT



Iron(III) chloride hexahydrate promotes a cascade of transformations on a Petasis condensation product that sets up the right dihydropyran precursors of valuable Relenza congeners.

Influenza A viruses cause a severe infection in the respiratory system and are responsible for seasonal epidemics and sporadic pandemics. Although the primary method for prevention is through vaccination, effective antiviral agents are required to prepare for a possible pandemic.[1]

Among anti-influenza drugs, selective inhibitors of the surface glycoprotein neuraminidase have been developed, and two of them, oseltamivir phosphate **1** (Tamiflu)[2] and zanamivir **2** (Relenza),[3] which mimick the high-energy oxycarbenium intermediate **3**, have been approved for human use. Most "anti-neuraminidase" strategies involve the use of oseltamivir,[4] but an alternative would be to use zanamivir analogues that resemble the natural substrate more closely.[5] The present work addresses this issue.

We report here a novel synthetic pathway combining the three-component borono-Mannich condensation (Petasis reaction)[6] with an efficient and selective iron(III)-promoted ($FeCl_3$•$6H_2O$) deprotection−cyclization one-pot process. Iron salts have recently attracted considerable attention as inexpensive and environmentally friendly agents in a wide range of selective processes in organic synthesis.[7] The result is a

[†] Institut de Chimie des Substances Naturelles.
[‡] Institut de Chimie Moléculaire et des Matériaux.

(1) (a) De Clercq, E. *Nat. Rev. Drug Discovery* **2006**, *5*, 1015–1025. (b) von Itzstein, M. *Nat. Rev. Drug Discovery* **2007**, *6*, 967–974.

(2) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681–690.

(3) von Itzstein, M.; Wu, W.-Y.; Kok, G. B.; Pegg, M. S.; Dyason, J. C.; Jin, B.; Phan, T. V.; Smythe, M. L.; White, H. F.; Oliver, S. W.; Colman, P. M.; Varghese, J. N.; Ryan, D. M.; Woods, J. M.; Bethell, R. C.; Hotham, V. J.; Cameron, J. M.; Penn, C. R. *Nature* **1993**, *363*, 418–423.

(4) Recent reviews on Tamiflu synthesis: (a) Farina, V.; Brown, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7330–7334. (b) Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, *2008*, 1827. (c) Magano, J. *Chem. Rev.* **2009**, *109*, 4398–4438.

(5) Collins, P. J.; Haire, L. F.; Lin, Y. P.; Liu, J.; Russell, R. J.; Walker, P. A.; Skehel, J. J.; Martin, S. R.; Hay, A. J.; Gamblin, S. J. *Nature* **2008**, *453*, 1258–1261.

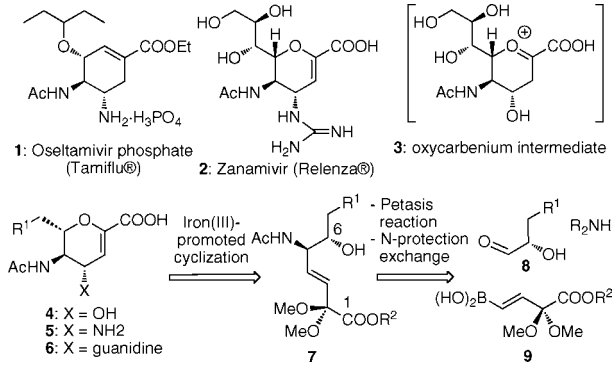
(6) (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583–586. (b) Petasis, N. A. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: New York, 2005; pp 1999−1223.

(7) For selected reviews, see: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254. (b) Diaz, D.; Miranda, P.; Padron, J.; Martin, V. *Curr. Org. Chem.* **2006**, *10*, 457–476.

10.1021/ol102326b
Published on Web 10/14/2010

very concise and high-yielding synthesis of constructs of the zanamivir family useful to explore the catalytic sites of the neuraminidases. Our retrosynthetic approach to zanamivir congeners **6** modified at the C6 position is outlined in Scheme 1. We envisioned acyclic derivative **7** with appropri-

Scheme 1. Structure of the Potent Neuraminidase Inhibitors Oseltamivir Phosphate **1** and Zanamivir **2** and Retrosynthetic Analysis of Zanamivir Congeners **6** from an α-Hydroxyaldehyde **8**

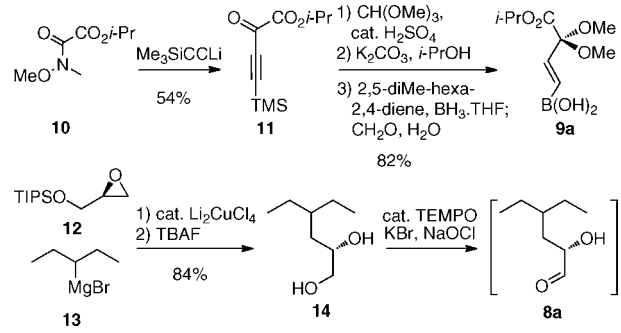


ate stereodirecting groups at either N5 or O6 as a key precursor to cyclic dihydropyrans **4**−**6** with the proper functionality and stereochemistry at C4. In turn, **7** could be derived from the Petasis condensation[8] using organoboronic acid **9** as the nucleophilic partner. This reaction performed with chiral α-hydroxyaldehydes **8** proceeds with a remarkably high stereocontrol, producing 1,2-aminoalcohols with an *anti* configuration.[9]

We first investigated the synthesis of a dihydropyran with an *iso*-pentyl side chain at C6 **4a**−**6a** (R^1 = $CHEt_2$), a substituent analogous to the Tamiflu hydrophobic side chain. The required building blocks were prepared from starting materials **10** and **12**,[10] respectively, as summarized in Scheme 2. The synthesis of boronic acid **9a** commenced by condensation of lithiated trimethylsilyl-acetylene on Weinreb amide **10**. The desired propargyl ketone **11** was quantitatively protected as a dimethylketal which was detrimethylsilylated by potassium carbonate in *i*-PrOH and efficiently hydroborated using di(isopropylprenyl)borane.[11] After oxidation, boronic acid **9a** was obtained in 82% yield.

The required α-hydroxyaldehyde (*S*)-**8a** was prepared from the protected (*R*)-glycidol **12**.[13] After epoxide ring

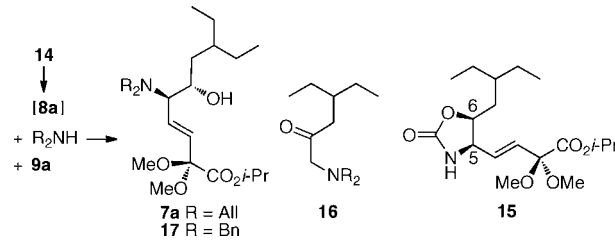
Scheme 2. Construction of Key Building Blocks Boronic Acid **9a** and α-Hydroxyaldehyde **8a**



opening with Grignard reagent **11a** in the presence of a solution of dilithium tetrachlorocuprate,[12] the resulting adduct was deprotected with TBAF to diol **14** in a good 84% yield over two steps. Diol **14** was then submitted to selective oxidation of the primary alcohol under biphasic conditions using a sodium hypochlorite solution in the presence of KBr and a catalytic amount of TEMPO, buffering with $NaHCO_3$.[13] Since this α-hydroxyaldehyde is difficult to characterize and purify, it was used directly after the oxidation workup in the next Petasis condensation.

In initial experiments of the Petasis reaction, using 1 equiv of each partner at room temperature with diallylamine in various solvents, the CH_2Cl_2/HFIP (9:1) system proved to be the most appropriate, providing aminoalcohol **7a** as a single diastereoisomer in a 41% yield (entries 1 and 2, Table 1). This modest result is explained by the formation of ketoamine **16** (21%) issued from an intermediate enamine.[14] A high yield of **7a** (95%) was produced with the use of an excess of aldehyde and amine (1.5 equiv of each) and heating

Table 1. Optimization of the Petasis Coupling Reaction of α-Hydroxyaldehyde **8a** with Boronic Acid **9a**



	amine	**8a**[a] (equiv)	solvent (temp °C)	*t* (h)	product	yield %[b]
1	$NHAll_2$	(1)	solvent[c] (22)	160−48[c]	**7a**	14−39[c]
2	$NHAll_2$	(1)	CH_2Cl_2/HFIP[d] (22)	24	**7a**	41
3	$NHAll_2$	(1.5)	CH_2Cl_2/HFIP[d] (80)	12	**7a**	95
4	$NHAll_2$	(1.5)	CH_2Cl_2, (120, MW)	0.25	**7a**	95
5	$NHBn_2$	(1.5)	CH_2Cl_2, (120, MW)	2	**17**	71

[a] Equiv of **8a** based on the starting diol **14**. [b] Isolated yield following chromatography, based on boronic acid. [c] Dioxane, 160 h, 14% yield; EtOH, 160 h, 19% yield; CH_2Cl_2, 48 h, 29% yield; toluene, 48 h, 39% yield. [d] As a 9/1 mixture. HFIP = hexafluoro-*iso*-propanol.

(8) For a recent use of the Petasis reaction in a de novo synthesis of the sialic acids, see: Hong, Z.; Liu, L.; Hsu, C. C.; Wong, C. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7417–7421.

(9) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798–11799.

(10) Lainé, D.; Fujita, M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1639–1646.

(11) Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3399–3404.

(12) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3125–3126.

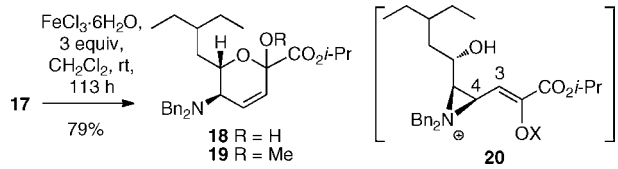
(13) (a) Lucio Anelli, P.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562. (b) Siedlecka, R.; Skarzewski, J.; Mlochowski, J. *Tetrahedron Lett.* **1990**, *31*, 2177–2180.

the reaction mixture at 80 °C for 12 h (entry 3). The reaction also proceeded smoothly in dichloromethane under microwave radiation (120 °C, 300 W, 15 min) (entry 4). Under these conditions, *N*,*N*-dibenzylamine also provided the expected adduct **17** in good yield (entry 5).[15] The stereochemistry of the *trans*-amino alcohol **7a**[16] was confirmed after removal of the allyl protecting group (*N*,*N*-dimethylbarbituric acid, cat. $Pd(PPh_3)_4$, CH_2Cl_2, 35 °C)[17] and conversion to the corresponding oxazolidinone **15** [$CO(OCCl_3)_2$, NEt_3, CH_2Cl_2, 87% from **7a**]. The ^1H NMR spectrum of **15** exhibits a coupling constant $^3J_{5,6}$ value of 8.0 Hz, indicating a *cis* relationship between H-5 and H-6.

Removal of the dimethyl acetal and cyclization proved extremely difficult. Treatment of **7** or **17** with a number of acidic promoters (H_2SO_4, TFA, $CeCl_3{\cdot}7H_2O/NaI$,[18] $Bi(NO_3){\cdot}5H_2O$,[19] $TiCl_4/LiI$[20]) in different conditions resulted in either no reaction or decomposition.

We ultimately found that treatment of amine **17** with iron trichloride hexahydrate in CH_2Cl_2 provided directly cyclic adducts **18**[21] and **19** (79% yield, ratio of 94:6) resulting from the deprotection of the acetal, double bond isomerization, and cyclization (Scheme 3). This expedient transformation

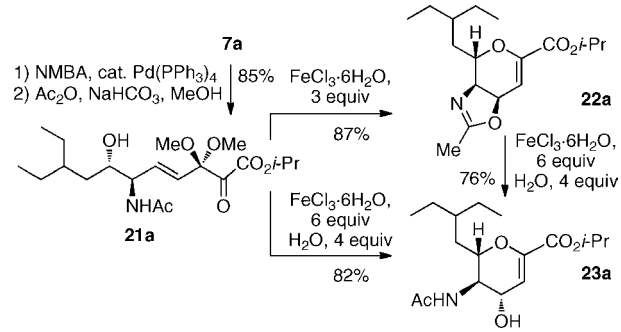
Scheme 3. Iron Trichloride-Promoted Cyclization of Tertiary Allylic Amine **17**



was however extremely sluggish (5 days with 6 equiv of $FeCl_3{\cdot}6H_2O$), and all attempts to further transform this tertiary amine never provided acceptable results. We believe that the double bond isomerization resulted from the formation of transient aziridinium intermediate **20** followed by rotation around the C3−C4 bond for cyclization.

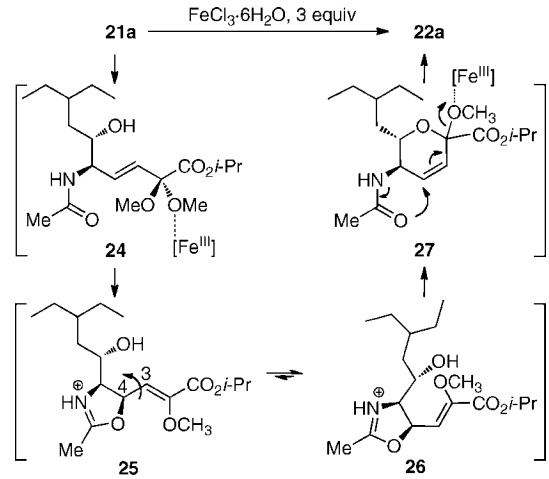
We then attributed the lack of reactivity to the absence of a good internal nucleophile under these conditions to participate in the cyclization process. For this, exchange of the *N*-dialkyl substituents to the natural acetamide was achieved on **7a** by palladium-catalyzed removal of the allyl protecting group and selective acetylation of the amino group to acetamide **21a** in 85% for the two steps (Scheme 4). With

Scheme 4. Iron Trichloride-Promoted Cyclization of Acetamide **21a** to Oxazoline **22a** and Alcohol **23a**



this change, we were pleased to find that $FeCl_3{\cdot}6H_2O$ now promoted cyclization smoothly (45 °C for 2 h) and unexpectedly provided directly allylic oxazoline **22a** as the only product (87% yield).[22] Moreover, adding water to the reaction medium led to the exclusive formation (82%) of alcohol **23a**, with the natural configuration of the sialic acids at C4. This may result from the in situ opening of oxazoline **22a** by water as shown by its transformation to **23a** under identical conditions.[23] A possible sequence could be an initial Lewis acid-assisted formation of oxazolinium intermediate **25** from complex **24** that rotates around the C3−C4 bond to **26** (Scheme 5). Cyclization to **27**, analogous to **19** (Scheme 3) and iron^{III}-promoted oxazoline formation, then leads to product **22a**.

Scheme 5. Iron Trichloride-Promoted Cyclization of Acetamide **21a**: Probable Sequence Leading to Oxazoline **22a**



(14) This side reaction reveals a poor reactivity of the boronic acid.

(15) With these optimized microwave conditions, the reaction with aminodiphenylmethane, a primary hindered amine that usually performs well in the Petasis reaction, did not afford the desired compound in a satisfying yield.

(16) Preservation of the enantiomeric purity was confirmed by chiral HPLC.

(17) Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109–6113.

(18) Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183–4184.

(19) Eash, K. J.; Pulia, M. S.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2000**, *65*, 8399–8401.

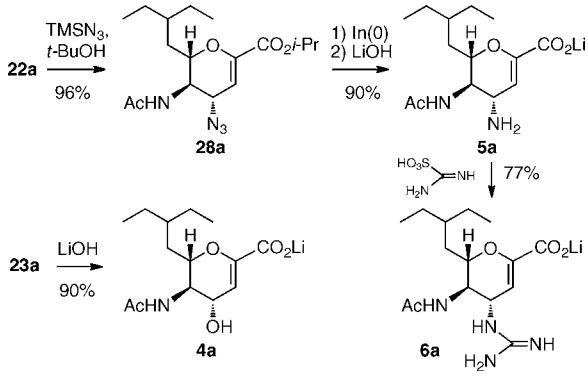
(20) Balme, G.; Gore, J. *J. Org. Chem.* **1983**, *48*, 3336–3338.

(21) As a 65:35 mixture of anomer in the favor of the β one, which was confirmed by a NOE effect between H-6 and the hydrogen of the hydroxyl proton at the C2.

(22) A similar oxazoline is in fact the key intermediate in the synthesis of zanamivir from Neu5Ac. See ref 5.

Introduction of nitrogen at C4 followed the previous reports in this area.[8] Opening of oxazoline **22a** with trimethylsilyl azide[24] gave azido compound **28a** selectively reduced with indium metal,[25] followed by saponification of the *iso*-propylester to furnish the corresponding amine **5a** (Scheme 6). Treatment with amino-iminomethanesulfonic

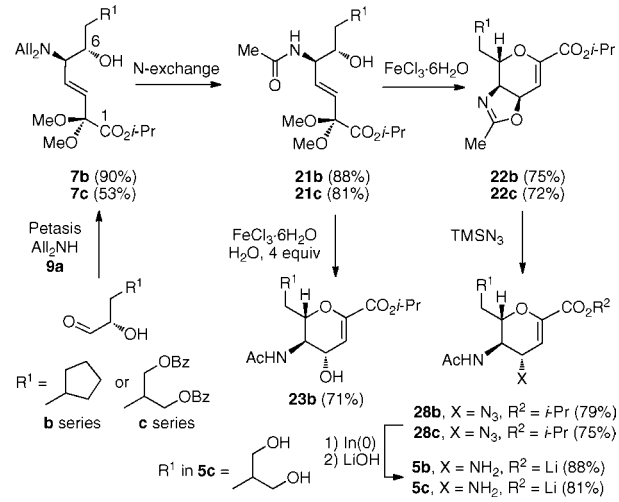
Scheme 6. Completion of the Synthesis of Zanamivir and 2,3-Unsaturated Sialic Acid (Neu5Ac2en) Analogues



acid[26] afforded the guanidine derivative **6a**, a zanamivir congener with a hydrophobic side chain at C6. An analogue of the 2,3-unsaturated sialic acid (Neu5Ac2en) was also obtained in the form of lithium salt **4a** by saponification of the *iso*-propylester **23a**.

We also briefly explored the efficiency of this newly developed synthetic sequence for the preparation of other Neu5Ac2en/zanamivir analogues. Thus, the above-mentioned synthetic route was successfully applied to aldehydes **8b** (R^1 = *cyclo*-pentyl) and **8c** [$R^1 = CH(CH_2OBz)_2$] (Scheme 7). The sequence involved the Petasis coupling (**7b** and **7c**), exchange of the protecting groups at nitrogen (**21b** and **21c**), iron(III)-promoted cyclization (**22b** and **22c**), azide formation (**28b** and **28c**), and reduction to amine/hydrolysis (**5b** and **5c**). The additional route by this iron(III)-mediated cascade

Scheme 7. Extension of the Synthetic Sequence for the Preparation of Zanamivir Analogues from Aldehydes **8b** and **8c**[a]



[a] Experimental details are given in the Supporting Information.

in the presence of limited amounts of water also provided the C4-alcohol **23b** in the *cyclo*-pentyl series.

In summary, we have developed a short synthetic route to the highly valuable dihydropyran framework of zanamivir congeners by coupling the Petasis three-component, boronic acid Mannich reaction to an iron(III)-promoted one-pot cascade of deprotection−C−C double bond isomerization−cyclization−oxazoline formation. Moreover, adding a limited amount of water to the iron promoter induced direct opening of the bicyclic oxazoline to Neu5Ac2en congeners in high yields. Additional flexibility of this synthetic approach is expected, especially in the development of novel preparations of structurally diverse ulosonic acids. This is currently being developed in our laboratory together with biological testing of the new constructs as antineuraminidases and anti-influenza agents.

Acknowledgment. This study was financially supported by the ICSN-CNRS.

Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102326B

(23) Treament of **21a** with HCl (18 equiv) replacing $FeCl_3 \cdot 6H_2O$ and water (4 equiv) under otherwise identical conditions (rt for 24 h) provided a complex reaction mixture from which oxazoline **22a** (14%) and a hemiacetal analogous to **18** (13%) could be isolated.

(24) von Itzstein, M.; Jin, B.; Wu, W.-Y.; Chandler, M. *Carbohydr. Res.* **1993**, *244*, 181–185.

(25) Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Tetrahedron Lett.* **1999**, *40*, 3937–3938.

(26) von Itzstein, M.; Wu, W.-Y.; Jin, B. *Carbohydr. Res.* **1994**, *259*, 301–305.